REMARKS

Claims 1-44 are pending. Claims 1 and 10 have been amended.

Claim 1 is amended to recite that the microgel can be encapsulated with a drug post polymerization and that the encapsulated microgel is injectable into the body. Support for the amendment is found in original claims 35 to 44 and in the specification on page 17 [0053], page 18, [0057] to [0060].

Claim 10 is amended to recite that the continuous phase employed in the inverse suspension process is a water immiscible solvent selected from the group consisting of heptane, octane, cyclohexane, toluene, dimethylbenzene, or a mixture thereof. Support for the amendment is found in the specification at page 15, [0045].

No new matter is introduced by the amendment. The amendment of claims 1 and 10 was discussed with the Examiner. Entry of the amendment is requested.

The Examiner has rejected the pending claims as obvious under 35 USC § 103(a) on two different grounds, each of which is responded to as follows. Reconsideration of the rejection is requested in view of the amendment of claims 1 and 10 and the claims dependent thereon and for the reasons stated below.

RESPONSE

Rejection over a combination of Pathak et el in view of Hirose et al and Dowding et al.

Claims 1-44 were rejected as being obvious over Pathak et al in view of Hirose et al and further in view of Dowding et al.

The Examiner contends that Pathak et al. US 6,201,065 discloses a multiblock hydrogels for drug delivery in aqueous solution and the method to produce them. The Examiner points to the disclosure that the hydrogel can be comprised of PEO-PPO-PEO block compolymerized with polylactuide, polyglycolide or polylactone. The Examiner agrees that Pathak et al. did not employ inverse suspension polymerization, but contends that Pathak et al. describes an aqueous normal suspension polymerization and further contends that the inverse suspension polymerization is merely a form of suspension polymerization.

The Examiner cited Hirose et al. for the proposition that the inverse suspension polymerization process is known for the production of microgel particles.

Previously, Applicant had pointed out that Pathak, et al. did not teach or suggest the use of inverse suspension polymerization nor recognized that by inverse suspension polymerization, it was possible to prepare a microgel that has far superior characteristics for drug loading and control release

Applicants wish to point out that the technique employed by Pathak et al. is known as solution or bulk polymerization. See Example 1, part a. which describes the systhesis of the acrylate encapped PEO-PPO-PEO monomer, wherein the starting materials F127-acrylate and the PEO-PPO-PEO were added to hot toluene. The turbid mixture was then filtered and added to hexane. The F127-(lactate)-acrylate macromer was synthesized by employing melt dried F127 and adding D,L-lactide to the melt. After a reaction of 4 hours, the melt was dissolved in toluene and then precipitated. Thus the process described by Pathak et al for forming the macromer is known as bulk polymerization. Bulk polymerization is not suspension polymerization.

The hydrogel was formed by using a solution of F127-(lactate)6- acrylate in PBS. The polymerization process is initiated by UV radiation to form a hydrogel. Thus, the macromer is dissolved in PBS as a solution and when polymerized precipitates out of solution. This is generally known as solution polymerization and not suspension polymerization, wherein the monomer is suspended as an oil droplet in the aqueous phase. The processes for forming other types of hydrogels described in the other examples are similar to that described in Example 1. Thus, contrary to the contention of the Examiner, Pathak et al. did not describe, teach or suggest suspension polymerization.

A combination of Pathak et al with Hirose et al. does not help. Hirose et al. used inverse emulsion polymerization, a process that is different from inverse suspension polymerization.

Hirose et al was cited for the proposition that it teaches that microgels can be made by inverse suspension polymerization.

Applicants have carefully reviewed HIrose et al. Hirose studies the phase transition behavior of a submicron IPA hydrogel bead. In column 2, paragraphs 2 and 3, Hirose et al. repeatedly stated that the process employed to prepare the IPA submicron gel beads is by inverse emulsion polymerization. Reversed emulsion polymerization is a different process from reverse suspension polymerization. The characteristics of the polymer formed from these two processes are quite different. Enclosed herewith is a copy of excerpts from three text books briefly distinguishing emulsion polymerization and suspension polymerization.

Seymour et al., Polymer Chemistry, An Introduction, pp303 – 305;

Hiemenz, P.C., Polymer Chemistry, The Basic Concepts, pp396 – 401;

Stevens, M.P., Polymer Chemistry, An Introduction, pp 196 – 199;

All three texts distinguishes suspension polymerization from emulsion polymerization because in emulsion polymerization, the polymerization process takes place in the micelles formed from using an emulsifying agent. Whereas, in inverse suspension polymerization, no micelles are formed, the polymerization takes place in monomer reservoirs suspended as droplets in the continuous phase. Because of the formation of a multitude of micelles, the particles formed by an emulsion process are 10^3 smaller than the particles formed in suspension polymerization. This is particularly true in inverse suspension polymerization. In Applicants' process, the water soluble monomer is suspended in a water immiscible solvent, e.g., heptane.

In addition, Hirose et al prepared an poly(isopropylacrylamide) gel (IPA gel). This is significantly different from the PEO-PPO-PEO – lactide – acrylate end capped microgel of the present invention. The IPA gel is not biodegradable. There is nothing in Hirose et al. that suggest that his method is applicable to a biodegradable gel which is sensitive to temperature.

The third reference Dowding et al. is cited for the proposition that heptane is well known for use as the continuous phase in inverse suspension polymerization.

Applicants wish to point out that Dowding et al. describes the swelling properties of a poly(NIPAM) minigel. This is an entirely different type of gel from the microgel of the present invention. It is to be noted that poly(NIPAM) is a stable polymer and is not biodegradable. There is nothing in Dowding et al. that suggests that the process he employed, inverse suspension polymerization, is applicable to a biodegradable polymeric material. There is no motivation for a person of skill in the art to employ a process for the preparation of poly(NIPAM) minigel to prepare a drug encapsulated microgel of the present invention that is biodegradable and with reverse thermosensitivity for the controlled release of the encapsulated drug.

Biodegradability of a polymeric material that is to be injected into the body is very important. As a sustained release carrier, the form and size of the micro particles formed are also very important for drug encapsulation. Conventionally, the pharmaceutical drug is mixed together with macromers and entrapped into the gel network during the formation of the gels by polymerization or crosslinking. The technique used in the present invention is by encapsulation of the drug after the gel is formed. This has several advantages such as the residue of un-reacted macromers and the solvents used are readily removed and encapsulation of proteins is easily accomplished without the use of a high temperature and any organic solvent which may denature drugs that are proteins. The micro particulate form enables an effective post-encapsulation encapsulation technique and also makes it possible to produce an injectable drug-loaded gel.

It is to be noted that Pathak et al. stated the hydrogel is formed in situ on the surgical site or the site for burn treatment. See column 9, lines 45-47 and Example 6. The drug loading and release experiments were carried out in vitro. Pathak also described a process by which the macromer solution, prior to the formation of the hydrogel is to be deposited by laparoscopy/endoscopy at a localized site and polymerized inside the body. See Column 12, lines 1-14. Repeatedly, Pathak et al. describes the need for on site polymerization of the macromer to form the hydrogel. For example, Pathak et al describes the application of the macromer "during surgery conducted through the cannula of a trocar." This means that the hydrogel is not formed, loaded with drug and then injected into the body. There is clearly no

teaching or suggestion that the drug loaded hydrogel is injectable. In fact even the macromer, prior to the formation of the hydrogel has to been introduced by laparoscopy/endoscopy or by means of a trocar.

Whereas, Applicant's invention is directed to a microgel prepared by inverse suspension polymerization. The polymerization method employed by Applicant provides a microgel that enables a unique post encapsulation technique employing the properties of the microgel. The drug loaded microgel is injectable. This shows that the microgel described and claimed by Applicant is structurally different from that of Pathak et al.

Claim 10 and the claims dependent thereon are directed to a reverse suspension process for the preparation of the microgel of the present invention. The rejection of amended claim 10 is requested in view of the amendment and for the reasons presented.

For the reasons stated above, and in view of the amendment of claims 1 and 10 and the claims dependent thereon, the rejection on this ground should be withdrawn.

Rejections under 35 U.S.C. §103 as obvious in view of a combination of Hubbell et al and Hirose and further in combination with Dowding et al.

Claims 1-34 rejected under 35 U.S.C. §103(a) as being unpatentable over Hubbell et al., US 6,306,922 in view of Hirose et al and further in view of Dowding et al..

The Examiner contends that Hubbell et al. disclosed aqueous hydrogels comprised of a water soluble PEO-PPO block copolymer linked with a biodegradable polylactide, polyglycolide or polylactone. The Examiner further contends that Hubbell et al. describes a hydrogel with a crosslinked copolymer that is the same as that of Applicants' invention and therefore should also be negatively temperature sensitive.

Applicant wish to point out that the Hubbell et al copolymer comprised polyethylene glycol (PEG) as a part of the copolymeric macromer. PEG comprise

hydroxyl groups to render the macromer highly water soluble. Thus, Hubbell et al employs photo initiation of the polymeric process by UV irradiation of an aqueous solution of the water soluble oligomers, principally comprising PEG end capped with glycolic acid oligomers. See Example 1. The macromer is precipitated upon cooling of the aqueous solution. Thus this is a solution or precipitation polymerization process.

The macromer was dissolved in methylene chloride and refluxed with acryloyl chloride and triethylamine. The solid triethylamine was removed and the polymer precipitated from the filtrate by adding excess hexane. Again, this describes a solution polymerization process.

A careful review of Examples 2, 3 and 4 shows that solution polymerization was employed in each case. Suspension polymerization employs a suspension of water droplets in oil or oil droplets in water. In Hubbell, neither type of suspension was described.

In addition, Hubbell et al. also disclosed or taught that the hydrogel is formed in situ on the tissue surfaces of a patient. There is no disclosure, teaching or suggestion that the precipitated hydrogel is injectable into the body. The type of application contemplated is to add a mixture of the drug with the macromers to the skin surface, irradiate the mixture with UV light to form the hydrogel. Moreover, the polymerization process employs organic solvents, such as benzene, methylene chloride, hexane which are detrimental to the body and cannot be injected as such.

The claims of the present application are directed to "A thermosensitive and biodegradable microgel"...that can be encapsulated with a drug post polymerization and the drug loaded microgel is injectable into the body (amended claim 1). In contrast, Hubbell, et al. described in situ polymerization wherein a mixture of the drug in an aqueous macromer solution is applied to the surface of the skin. The microgel of the present invention are formed by inverse suspension polymerization. This process is different from the solution polymerization process disclosed in Hubbell, et al. Thus, the microgel of the present invention is clearly distinguishable

from Hubbell et al. for the reasons stated above and is not obvious in view of Hubbell et al..

A combination Hirose et al and Hubbell does not help. As stated above, Hirose et al employed inverse emulsion polymerization to copolymerize IPA. This is clearly not a thermosensitive, biodegradable microgel injectable into the body as described and claimed in the present invention.

The further combination of Dowding does not help. As stated above, Dowding et al. disclosed a poly(NIPAM) minigel. The non-biodegradable, non-thermosensitive minigel of Dowding is entirely different from that of the Applicant's invention as claimed.

Thus the rejection of claims 1-34 in view of Hubbell et al. in combination with Hirose et al. and Dowding et al. should be withdrawn.

In conclusion, the claims of the present application are mainly directed to a specific thermosensitive and biodegradable microgel that is injectable into the body (claim 1), the method of preparation thereof (claim 10), and a simple method of loading a substance into a network of the microgel with negative temperature sensitivity (claim 35). The claimed invention is different from that of an *in situ* encapsulation technique, wherein the un-reacted macromers or impurities remain in the encapsulated hydrogel. The invention as claimed enables the encapsulation of the drug after removal of most of the remaining un-reacted macromers in hydrogel. It also avoids the use of organic solvents and high temperature in the loading of a proteinaceous drug. The claimed microgel, the methods of preparation thereof and the post-fabrication encapsulation method are unique and should be patentable.

CONCLUSION

As amended it is believed that the claims presently presented are allowable. An early allowance is earnestly requested.

The amendment and the analysis of the prior art processes were discussed with the Examiner. Claims 1 and 10 were amended at the suggestion of the Examiner, who indicated that as amended the claims are directed to an invention

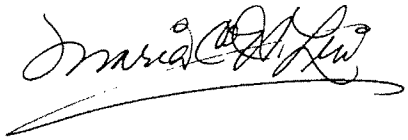
and are allowable. An early allowance is requested. The courtesy of the Examiner extended during the telephone interview is deeply appreciated.

A summary record of the interview is enclosed.

AUTHORIZATION

Applicants believe that no additional fees are necessary, however, should any such fees be due, the Commissioner is hereby authorized to charge any additional fees which may be required for this Amendment, or credit any overpayment, to Deposit Account No. 13-4500, Order No. 4614-4000.

Respectfully submitted,



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